

The Relationship Between Blood Lead and Blood Pressure in the NHANES II Survey

by Joel Schwartz*

A large body of experimental data has shown that lead raises blood pressure and increases responsiveness to α -adrenergic agonists in rats and pigeons. These studies suggest the need to look for a similar relationship in humans. This paper examines the robustness of the previously reported association between blood lead and blood pressure in adult males. The association remains strong and is essentially unchanged in tests that include nutritional factors and demographic factors, alone or together, or in tests that include insignificant terms. The relationship was not confounded by age; it held for all adult men in the 20-45 age group, the 40-59 age group, and the 46-74 age group. Interaction terms for 25 30-year age groups (20-49, 21-50, . . . , 45-74) were all insignificant, indicating no difference in the relationship by age. The relationship is also robust to the inclusion of a time trend to account for possible omitted time-varying factors, and it held in a model that controlled for possible site effects. Given the strong experimental evidence, the relationship is likely causal.

Introduction

Recent experimental evidence has demonstrated that moderate levels of lead cause elevations in blood pressure in animals (1-6). These findings show effects at varying doses and across species and indicate possible modes of action for lead that involve general mechanisms operant across all animal species.

For instance, both Iannoccone et al. (1) and Carmignani et al. (2) have reported *in vivo* studies showing that lead-exposed rats had increased response to α -adrenergic stimulation. These results have been reported *in vitro* by Webb et al. (4), using arteries from rats that had been exposed *in vivo*. Such activity would be expected to lead to increases in blood pressure. Skoczynska et al. (7) also reported that lead-treated rats had augmented and prolonged pressor responses to epinephrine and norepinephrine, less pronounced depression of arterial pressure in response to isoproterenol, and more pronounced tachycardia in response to isoproterenol. Skoczynska et al. also found in perfusion studies of isolated arteries that lead caused more pronounced vasoconstriction in response to norepinephrine.

Of particular interest, Piccinini and Favalli (8) have reported that the addition of lead to the media of perfused isolated rat tail arteries led to contraction and to hyperreactivity in response to stimulation. The exposed arteries had higher levels of cytosolic calcium

than the control group, consistent with other findings of lead causing a calcium leak into cells (9). Lead has been found to contribute to increased intracellular concentrations of calcium in brain capillaries (10), neurons (11), osteoclasts (12), and hepatocytes (13). As increased intracellular calcium is the trigger for smooth muscle contraction, these results again suggest a biological mechanism for an effect of low-level lead exposure on blood pressure.

In addition, Goldstein and Ar (14) have reported that lead activates calmodulin in its role of activating phosphodiesterase, the enzyme that converts cyclic AMP into AMP. Cyclic AMP is involved in stimulating the calcium pump that removes calcium from the cytosol into the endoplasmic reticulum and also leads to the phosphorylation of myosin light-chain kinase, reducing its sensitivity to activation by calcium. These are actions that would be expected to reduce reactivity and tone, and a lead effect on cyclic AMP represents a potential adverse disturbance of these processes.

Finally, the experimental literature suggests a nonlinear relationship, with effects on blood pressure primarily at the lower blood lead levels. Pounds (13) reported that low-level exposure to lead caused increased accumulation of calcium in all of the compartments of the cell, whereas at higher lead exposure, the two shallower compartments, including the cytosol, saturated out, and calcium accumulation continued only in the deepest compartment, thought to be the mitochondria. Thus, the hypothesis that lead increases blood pressure by disturbing cytosolic cal-

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cium metabolisms appears consistent with this non-linearity in response.

In light of this finding of an effect and possible mechanism, we examined a large representative survey of the U.S. population for a relationship between blood lead and blood pressure. Some of these analyses have previously been reported (15,16).

The Second National Health and Nutrition Examination Survey (NHANES II) was conducted between February 1976 and February 1980 on a sample chosen to be representative of the civilian, noninstitutionalized U.S. population aged 6 months to 74 years. A total of 20,322 persons were examined, and blood lead determinations were obtained for a representative subsample of 9932. The medical evaluations included medical history, physical examination, anthropometric measurements, dietary information (24-hr recall and food frequency), laboratory tests, ECGs, and radiographs. Special interview and examination protocols and specifically trained interviewers and examiners were used to ensure standardized conduct of the survey at each site. The nutrient intake from the 24-hr recall was quantified for each individual using a current nutrient data bank.

Blood samples were analyzed by the Clinical Chemistry Division, Centers for Disease Control. Blood lead concentrations were determined by atomic absorption spectrophotometry using a modified Delves Cup micromethod (17). Both bench and blind quality controls were used.

The analysis of the relationship between blood lead and blood pressure is confounded by age. Both lead and blood pressure increase with age. Moreover, studies of populations not exposed to the environment of western civilization, both in Africa and the Pacific Islands, as well as in isolated communities in Wales, show that blood pressure does not increase with age. Thus, age must be treated not as representing a marker for the aging process, but rather as representing unknown stresses, and the cumulative effect of elements of the western environment. Lead is one of these elements, and thus the confounding is real. To minimize that confounding we have adopted several approaches. First, we performed analyses in the 40- to 59-year-old age group, the age group with the lowest correlation between blood pressure and age. Second, we have repeated the analyses for all men aged 20 to 74, with the expectation that the large sample size will partly mitigate the confounding. Finally, we have repeated our analyses with interaction terms for different age groups, to test for the uniformity of the effect across ages without paying the sample size penalty that subsampling entails.

Initial Analysis

40- to 59-Year-Old Cohort

The established correlates of blood pressure are age, sex, race, and obesity. We used Quetelets body mass

index (BMI) (weight/height²) as the principal obesity measure in this analysis. For the 40- to 59-year-old age group we only considered white males. We forced age into the models in order to avoid any upward bias in the lead coefficients.

The natural log of blood lead was more normally distributed, more significant, and gave a higher R^2 than untransformed blood lead, blood lead squared, blood lead + blood lead squared, the square root of blood lead, or blood lead to other fractional powers (we examined 0.15, 0.2, 0.3, and 0.4). All of the results reported here are for the natural log of blood lead, but regressions for untransformed lead gave very similar results.

The initial regressions analyzed systolic and diastolic blood pressure for white males, 40 to 59 years old, with a model consisting of age, age squared, BMI, and blood lead. These regressions were done to determine whether blood lead levels were significantly associated with systolic and diastolic blood pressure after controlling for the well-documented correlates of blood pressure. Lead was statistically significant ($p < 0.01$) for both systolic and diastolic blood pressures in all OLS (ordinary least squares) regressions, in weighted regressions, and in weighted regressions with the design effects of the survey.

Tests of Robustness

The regression models were then expanded to incorporate additional variables, with particular attention directed to the stability and significance of the lead coefficient in the presence of nutritional factors and blood biochemistries.

A large set of nutritional and biochemical variables from NHANES II was included in stepwise regressions. The large set was used because blood pressure is such a multifactorial outcome and because we desired to test the robustness of the lead relationship to the inclusion of other variables, and the reporting of significance for any of them in these analyses should not be taken as an endorsement of a relationship. In addition, a large set of demographic and personal history variables was also considered in stepwise regressions.

Nutritional and Biochemical Variables

To provide an unusually rigorous test of the independent significance of blood lead, almost all of the nutritional and biochemical variables in the NHANES II were included in stepwise regressions. In addition, to account for possible curvilinear relationships, squared and natural logarithmic transformations of these variables were also included. The variables are listed in Table 1. The objective was not to evaluate the possible association of nutritional or biochemical measurements with blood pressure, but rather to conservatively estimate the strength and independence of the relationship between blood lead and blood pressure.

Table 1. Variables included in the stepwise regression analysis.

Age ^a	Dietary iron ^b
Age ^{2a}	Dietary vitamin A ^b
Body mass index	Dietary vitamin C ^b
Dietary sodium ^b	Dietary thiamine ^b
Salt-shaker sodium	Dietary riboflavin ^b
Dietary sodium × salt-shaker sodium	Dietary niacin ^b
Dietary potassium ^b	Serum cholesterol ^b
Dietary sodium- potassium ratio	Serum vitamin C ^b
Dietary calcium ^b	Serum iron ^b
Dietary phosphorus ^b	Serum transferrin saturation
Dietary protein ^b	Serum zinc ^b
Dietary fat ^b	Serum copper ^b
Dietary carbohydrate ^b	Serum albumin ^b
Dietary cholesterol ^b	Hemoglobin ^b
Dietary saturated fatty acids ^b	Red blood cell count
Dietary oleic acid ^b	Ethanol consumption/week ^b
Dietary linoleic acid ^b	Cigarettes smoked/day
	Total dietary grams ^b
	Total dietary calories ^b
	Cigar or pipe smoking

^aForced into each regression to remove any possible age effects on blood pressure.

^bThe natural log and squared transformation of these variables were also included in the stepwise regression.

Including these additional 87 variables increases the probability of variables being found statistically significant due to chance alone. This complicates the interpretation of nutritional and biochemical factors, but not the interpretation of the lead variable; it only makes it more difficult for lead to maintain its significance.

The general procedure for variable selection was as follows: First, weighted, stepwise multiple linear regression was used to determine which variables were significantly related ($p < 0.05$) to blood pressure (using the MAXR options of the SAS procedure Stepwise). The MAXR procedure determines for any given model size (i.e., number of independent variables) the variables that explain the greatest amount of the variance of blood pressure. We chose the largest model with all variables significantly related to blood pressure ($p < 0.05$). From the 87 nutritional and biochemical variables, the weighted, stepwise regression selected 5 additional variables for diastolic pressure and 6 additional variables for systolic pressure, using the 5% significance test. These were used as the starting model for the SAS procedure SURREGR, which incorporates the survey design effects. For both systolic and diastolic blood pressures, one variable from the weighted stepwise regression failed to maintain significance at the 5% level after the design effects were incorporated. The final regression results for systolic and diastolic pressures, after accounting for the weighting and design effects, are given in Table 2.

To investigate whether a threshold level, below which no effect of blood lead on blood pressure existed, piecewise linear regressions were performed using the SAS procedure NLIN. These segmented regressions fit two lines to the data. One, below the putative blood lead threshold T , depends on all the variables except lead. The other, for blood lead levels above T , includes lead.

Table 2. Regression of diastolic and systolic blood pressures in white males age 40 to 59.

Variable	Coefficient	t-Statistic	Probability
Diastolic			
Age	0.2768	0.17	0.8636
Age ²	-0.0014	0.10	0.9321
Body mass index	1.131	8.55	0.0001
Log(blood lead)	3.954	2.85	0.0080
Dietary potassium	-0.0018	4.92	0.0001
Hemoglobin	1.548	3.90	0.0005
Albumin	3.587	2.50	0.0179
Log(dietary vitamin C)	1.838	4.65	0.0001
Systolic			
Age	1.311	0.57	0.5720
Age ²	-0.0068	0.30	0.7706
Body mass index	1.736	9.42	0.0001
Log(blood lead)	8.436	3.24	0.0028
Albumin	7.088	2.50	0.0178
Log(dietary vitamin C)	2.411	3.84	0.0005
Log(dietary riboflavin)	-5.509	3.07	0.0044
Log(dietary oleic acid)	3.992	2.49	0.0183
Log(serum vitamin C)	-3.472	2.47	0.0184

We used an iterative algorithm that chooses the threshold point that minimizes the sum of the squares of the errors over the full range of blood lead levels.

After including the nutritional variables, the blood analytes, and their curvilinear transforms, blood lead remained significantly associated ($p < 0.05$) with both systolic and diastolic blood pressures. The coefficient of lead in the regressions was within 10% of the original value. Further, the segmented regression analysis indicated that there was no threshold blood lead level in the relationship.

Interaction Terms

In multiple regression analysis, another consideration is the possibility of significant interaction terms. To evaluate this possibility, an additional weighted, stepwise regression analysis was done for both systolic and diastolic blood pressure. The new variables consisted of the linear interaction terms between the final variables in the model (shown in Table 2) and the linear form of all the other variables originally considered for the initial stepwise regression (Table 1). This meant running a stepwise regression with 162 interaction terms added to the final regression models for systolic and diastolic blood pressures. Using such a large set of variables gave a high probability that some variables would enter at the 5% level by chance. However, the purpose was not to determine if these variables were independently significant, but rather to further test the significance and independence of the relationship between blood pressure and blood lead. As expected, several interaction terms entered the systolic and diastolic regressions, but in each regression the lead coefficient varied less than 10% from its original value and remained significant ($p < 0.015$).

Marginally Insignificant Variables

Three other analyses were done to ensure that this relationship was robust. First, the original weighted, stepwise regression was extended to include variables significant through the 15% level to see if marginally insignificant variables influenced the significance of lead. For both systolic and diastolic pressures, lead remained significant and there was little change in the magnitude of the coefficient (less than 10%).

Second, for diastolic blood pressure, all the variables were included that were significant between the $p = 0.05$ and the $p = 0.15$ levels, and every possible combination of those variables (taken 1, 2, 3, 4, 5, 6, 7, and 8 at a time) was considered. All 255 combinations were added to the variables that were significant at the 5% levels, and a regression was performed on each set. The coefficient of blood lead varied by only +10% to -10% from the value that we obtained when we only included significant variables, and lead was always significant ($p < 0.01$). This analysis was not repeated for systolic blood pressure.

The last analysis was the most demanding test of the independence of the relationship between blood pressure and blood lead. Models for systolic and diastolic blood pressure were fit by weighted, stepwise regression using the original candidate variables (Table 1) but excluding lead. This gave all of the other variables and their curvilinear transformations the maximum opportunity to explain variation that could also be explained by lead. After obtaining these new, final models, a single regression for each outcome was run adding the lead variable to the variables of this model. For both systolic and diastolic blood pressures, lead was still statistically significant ($p < 0.016$) and the magnitude of the lead coefficient changed less than 10% from those obtained in the original analyses.

Because some people have found that small amounts of ethanol are associated with reduced blood pressure, ethanol was also modeled as a quadratic function of alcohol consumption, and also with two dummy variables for low and high consumption. The stepwise regression was repeated, and results did not change. The results of these analyses indicate that the strength and independence of the relationship between blood lead pressure was remarkably stable.

Demographic and Personal History Variables

We next considered the possibility that inclusion of the variables shown in Table 3 would affect the stability of the lead regression. Hypertension medication and low salt diet were tested to see if the response to lead was altered by these factors. The inclusion of these factors and interaction terms between them and lead did not change the lead coefficient appreciably, and the interaction terms were insignificant. As hypertension medication is a marker for high blood pressure, its

Table 3. Nonnutrition variables tested in the stepwise regression.

Variables	Other personal history variables
Demographic	Tricept skinfold
Family income	Subscapular skinfold
Poverty index	Recreational exercise
Region of the country	Work-related exercise
Season of the year	Recent weight loss
Degree of urbanization	Family history of hypertension
Residence inside central city	Kidney disease
Educational level	Serum creatinine
Hypertension	
Hypertensive medication	
Low salt diet	

inclusion in a model is not very informative. All of the subsequent analyses were performed with and without the inclusion of hypertension medication.

The other variables in Table 3 were tested in two ways. First, the stepwise regression procedure was repeated using the variables in Table 3 and only the nutritional and biochemical variables that had been significant at the 15% level in the previous analysis. Again, lead was selected for both systolic and diastolic blood pressure ($p < 0.005$) and its coefficient was within 10% of the original model that contained only age, age² and body mass index.

The variables in Table 3 were then added to all of those in Table 1, including their curvilinear transformations, and the stepwise process was repeated, yielding the same results. Finally, we re-ran the stepwise regression using all of the variables in Tables 1 and 3 except for lead, allowing maximum opportunity for colinear factors to enter. Lead was then inserted in the resulting models for systolic and diastolic blood pressure. It was still significant ($p < 0.01$) with less than a 10% change in its coefficient. In addition, smoking and drinking were forced into the regression models, and lead remained significant ($p < 0.01$), with no noticeable change in its coefficient.

Previous analyses have shown that about half of the lead in people in the NHANES II sample came from gasoline (18,19). Tetraethyl lead has little cadmium contamination, so confounding with cadmium is unlikely. However, occupationally exposed workers are also exposed to cadmium, so we repeated the regression excluding all persons in job categories cited by NIOSH as having potential lead exposure. Lead remained significant for both systolic and diastolic blood pressure ($p < 0.01$).

Principal Components Analyses

Because nutritional variables are often colinear with each other and may in fact only be important in complexes, a second approach was taken to dealing with nutritional and serological variables. Principal components analysis was done to find the linear combinations of the nutritional and serological factors that explained the greatest amount of their common vari-

ation. These principal components were then entered into the stepwise regression to allow those factors to explain a greater amount of the variation in blood pressure before colinearity prevents any more variables from entering. For instance, the first five principal components of the variables in Table 1 explain 50% of their variation. When these principal components were used instead of the raw variables and the stepwise regression was repeated, lead again was significantly associated with both systolic and diastolic blood pressure ($p < 0.01$), and its coefficient was changed by less than 10% from its original value.

Colinearity and Influence Diagnostics

Although all of these analyses make it clear that colinearity is not the cause of lead's correlation with blood pressure, variance inflation factors were computed for our final models. No significant variable had a variance inflation factor above 1.4.

To ensure that the significance of lead in the regression was not due to the presence of a few influential observations, influence diagnostic procedures were run. Residuals were plotted for all the observations, and the largest residuals were clustered near the middle of the data, where their influence is slight. Cook's D statistics, a standard measure of an observation's influence on a regression, were also computed for each observation. The highest Cook's D was 0.029 and the second highest was 0.023, both of which are very small. Moreover, of the 10 observations with the largest Cook's D statistics, 6 had positive residuals and 4 had negative residuals, indicating that the most influential observation's split almost evenly on how they would influence the lead coefficient. Figures 1 and 2 show the relationship between blood lead and both systolic and diastolic blood pressure in this population, after adjusting for all of the other significant covariates.

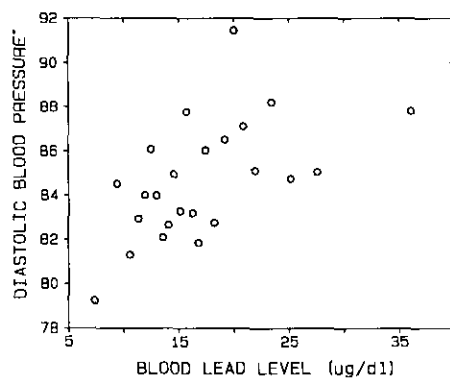


FIGURE 1. Adjusted diastolic blood pressure and adjusted blood lead levels for white males age 40 to 59. Both blood pressure and blood lead have been adjusted by regression for the effects of age, age², body mass, and other significant variables listed in Tables 2 and 3. Each point represents the mean blood pressure and mean blood lead for 24 consecutive observations, sorted in increasing order of blood lead.

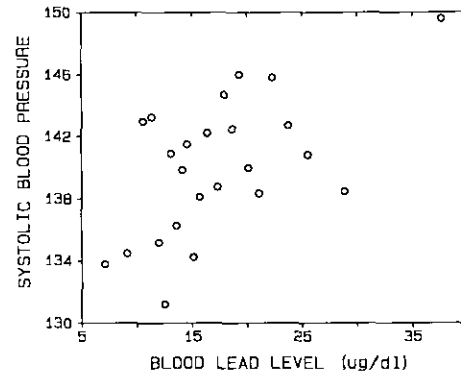


FIGURE 2. Adjusted systolic blood pressure and adjusted blood lead levels for white males age 40 to 59. Both blood pressure and blood lead have been adjusted by regression for the effects of age, age², body mass, and other significant variables listed in Tables 2 and 3. Each point represents the mean blood pressure and mean blood lead for 24 consecutive observations, sorted in increasing order of blood lead.

Results for All Adult Men

The 40- to 59-year-old age group represents about one-third of adult males and is the only group where the confounding of age and blood lead can be eliminated unambiguously. Additional regressions were performed, however, to confirm the relationship in the full population of adult men (> 20 years of age). Again, our analysis began by looking at the basic variables clearly linked to blood pressure: age, race, and body mass. Age was again modeled with both a linear and quadratic term to account for the nonlinear dependence. In this analysis, blacks were included, and a dummy variable for race was included in the regression because the sample size was now large enough to permit separating the race effect. Lead was once more found to be a significant predictor of both systolic and diastolic blood pressure ($p < 0.01$).

Tests of Robustness

We next included all of the variables in Table 1 and Table 3, along with their square and log transforms, in a stepwise regression analysis, to test whether inclusion of these other variables could affect the lead-blood pressure relationship. Lead was selected as significant for both systolic and diastolic blood pressure ($p < 0.01$). This result held whether or not hypertensive medication was included in the stepwise regression. Figures 3 and 4 show the relationship between blood lead and both systolic and diastolic blood pressure in all adult men after controlling for all covariates.

To assure that lead was not acting for a variable that did not enter the regression because it was colinear with lead, we re-ran the stepwise regression using all of the variables in Tables 1 and 3 except for lead. Lead was then inserted in the resulting model and its significance checked. Lead was significantly related to both systolic and diastolic blood pressure ($p < 0.01$).

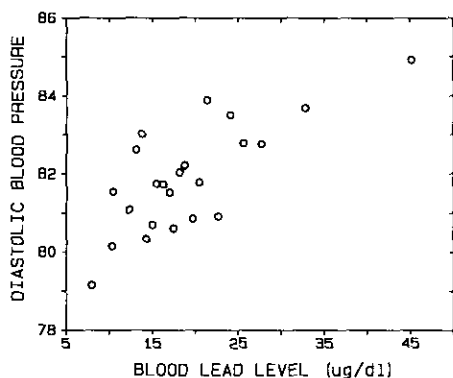


FIGURE 3. Adjusted diastolic blood pressure and adjusted blood lead levels for males age 20 to 74. Both blood pressure and blood lead have been adjusted by regression for the effects of age, age², body mass, and other significant variables listed in Tables 2 and 3. Each point represents the mean blood pressure and mean blood lead for 50 consecutive observations, sorted in increasing order of blood lead.

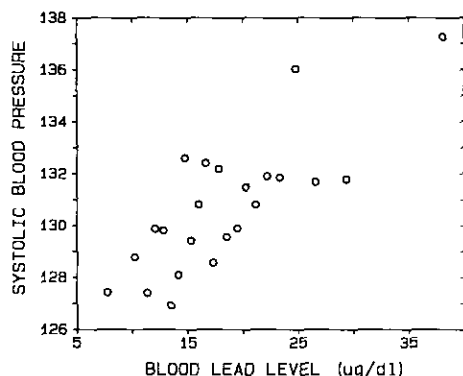


FIGURE 4. Adjusted systolic blood pressure and adjusted blood lead levels for males age 20 to 74. Both blood pressure and blood lead have been adjusted by regression for the effects of age, age², body mass, and other significant variables listed in Tables 2 and 3. Each point represents the mean blood pressure and mean blood lead for 24 consecutive observations, sorted in increasing order of blood lead.

Interactions with Hypertension or Hypertensive Medication

To assure that a spurious correlation was not occurring due to an interaction of lead levels with hypertensive medication or due to kidney disease elevating both blood pressure and blood lead levels, several additional analyses were performed. The stepwise regressions were repeated excluding all persons on hypertensive medication. Again, all variables in Table 1 were considered, not to determine whether they were true predictors of blood pressure, but to allow maximum possibility for another factor to explain the correlation between blood pressure and lead. Lead was significantly related to both systolic and diastolic blood pressure ($p < 0.01$). Serum creatinine was forced into the regression, and lead remained significant ($p < 0.01$).

Next, the stepwise regression was repeated including hypertensive medication as a variable. Lead was again selected for both systolic and diastolic blood pressure ($p < 0.01$), and an interaction term between lead and hypertensive medication was not significant. Finally, all men with diastolic blood pressure above 90 mm Hg were excluded from the sample, and the stepwise regression was repeated. Lead was again chosen as significantly related to both systolic and diastolic blood pressure ($p < 0.01$).

Other Age Groups

The most robust way to check for a differential lead effect in different age groups is to use interaction terms, thereby maintaining sample size. We used dummy variables for the age groups 20 to 39 and 60 to 74 and interaction terms between them and lead. The interaction terms were highly insignificant ($p > 0.35$), indicating the same magnitude effect in all ages.

As a further check, we separately ran the stepwise regression, using all of the variables in Tables 1 and 3, for the age groups 20 to 45 and 45 to 74. The larger age groups were used to compensate for the increased colinearity with age. Lead was chosen as significant for both age groups, for both systolic and diastolic blood pressure. Next, the regression for all adult males was repeated, but an interaction term for the 25 sequential age groups (20–49, 21–50, . . . , 45–74) was tested in 50 separate regressions (one for each age group, for both diastolic and systolic blood pressure). Lead was significant in each regression, and the interaction term was insignificant, again indicating a uniform relationship in all age groups. Finally, the regressions for both systolic and diastolic blood pressure were repeated in each of the 25 age groups, and lead was significant in all 50 regressions. Figure 5 shows the coefficients of diastolic blood pressure plotted against the median age for each of the 25 subgroups. The slope appears lower, although insignificantly so, in the youngest age groups. For the remaining 20 age groups, the slope oscillates about a mean of approximately 3.4 (on the log scale), indicating that a drop in blood lead levels from 18 $\mu\text{g/dL}$ to 10 $\mu\text{g/dL}$ would reduce diastolic blood pressure by 2 mm Hg.

Time Trends

The introduction of unleaded gasoline in 1975 created a time trend in blood lead levels in the United States. This downward trend accelerated in 1978 when further regulations restricted the amount of lead in leaded gasoline. Since the NHANES II blood lead data was collected from February 1976 to February 1980, there is a time trend in the blood lead data. If there were a time trend in blood pressure because of another factor, and that factor were omitted from the analysis, this would confound the relationship. Examination of the blood pressure levels in the National Health Survey in

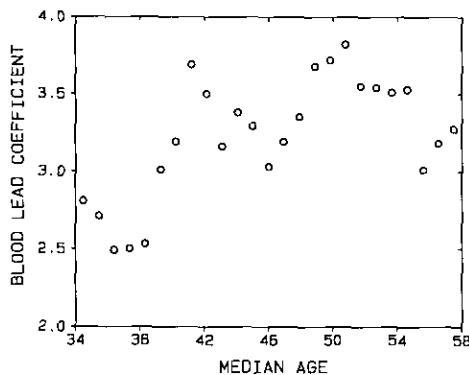


FIGURE 5. Coefficient of log blood lead (in a regression for diastolic blood pressure) versus median age for the 25 subgroups.

the 1960s, in the NHANES I from 1971 to 1975, and in the NHANES II, show that levels in NHANES II were the same as in the 1960s but somewhat lower than in NHANES I. Thus, no clear trend in blood pressure over time is evident. The data are qualitatively suggestive of the relationship we have found within the NHANES II survey, since gasoline lead use peaked during the period of the NHANES I survey. Nevertheless, it is important to make sure that the relationship we have identified is not confounded.

Other Covariates That Might Change Over Time. Time trends in other causal factors of blood pressure will only confound the analysis if those factors are omitted, and the first approach is to include them. Obesity, exercise, diet, serum cholesterol levels, smoking, etc., are all included in the model; changes in these factors will not confound the lead relationship. The dietary variables are sensitive enough to measure, e.g., changes in saturated versus polyunsaturated fats in the diet. Increased use of hypertensive medication over time was similarly controlled for, and in fact, no major external determinant of blood pressure has been omitted from the analysis, making confounding unlikely.

Modeling Time Trend. Because blood lead levels fell at a much faster rate in the last 2 years of the NHANES II survey, the slope of the correlation between blood lead and an omitted time-dependent covariate would have changed in the second half of the survey. If the correlation between blood lead and blood pressure was due to blood lead correlating with this omitted covariate because both of them have a time trend, then the slope of the blood lead-blood pressure relationship would also change in the second half. We tested this by entering an interaction term in our model. The interaction term was highly insignificant ($p = 0.75$ systolic, $p = 0.79$ diastolic), indicating that the major change in the decline of blood lead over time was not accompanied by any change in the relationship with blood pressure.

Next, we inserted a term for time into our model for all adult men and re-estimated. Lead was again significant as a predictor of both systolic and diastolic

blood pressure ($p < 0.05$). We concluded that an omitted time trend is not confounding this analysis.

Geographical Variation

Since the survey took data in 64 locations, it is possible that there are design effects in the data. The SURREGR regression package that we used accounts for the design effects by estimating the covariance using a Taylor series approximation for the off-diagonal effects. An alternative is to assume a different intercept for each sampling unit. This also examines the time trend issue in a different way. As the sites were sampled at different times, the different site intercepts represent either site or time differences. As the 64 PSUs were randomly selected from candidate PSUs to represent the U. S. population, we have used a random effects model (20). Using this model to include site effects, we found that lead was still a significant predictor of both systolic and diastolic blood pressure ($p < 0.05$) for both all adult males and the 40- to 59-year-old age group. The regression coefficients are reduced about 25% in these models. We conclude that the relationship is not confounded by either site or time effects.

Conclusions

There is a robust relationship between low-level lead exposure and blood pressure in the NHANES II data. This relationship holds whether we only examine the age group with minimal age confounding or whether we examine all adult men. It is not confounded by any plausible dietary, demographic, or anthropometric variables. It holds after controlling for the time trend in the data and may be the cause of that trend.

The animal evidence clearly indicates a causal relationship between lead exposure and blood pressure in several species. The animal data also show that lead interferes with cellular calcium metabolism in ways that would be expected to increase blood pressure; these mechanisms also regulate blood pressure in humans.

Essentially all of the recent human studies have found a positive association between blood lead and blood pressure. In most of the studies the association has been significant, in some of the others the magnitude of the insignificant association was similar to the magnitude in the significant findings. Although most of the studies have been in men, recently Rabinowitz et al. (21) have reported that umbilical cord blood lead was significantly associated with both blood pressure at delivery and the presence of pregnancy hypertension in a sample of 3200 live births in Boston with low lead levels (mean blood lead = $6.9 \mu\text{g/dL}$). Given these results and the strength of the animal models, the conclusion that there is a causal association seems warranted.

Small changes in blood pressure, even at levels below those defined as hypertension, were associated with

increased risk of heart attacks, strokes, and deaths in the Framingham study (22). While studies such as these can only inferentially implicate lead in these serious outcomes, the likelihood that lowering blood pressure reduces those risks is considered high enough to warrant giving drugs with serious side effects to persons with diastolic blood pressure above 90 mm Hg. It seems prudent to also recommend that reduction in exposure to a toxic substance that raises blood pressure is also warranted. Moreover, while these data do not allow a direct assessment of the effect of lead on cardiovascular deaths, there are two recent studies that addressed that issue. Khera et al. (23) found significantly higher levels of blood and urine lead in hospital outpatients being treated for hypertension or cardiovascular disease than in controls. Voors et al. (24) found a highly significant association between lead levels in the aorta of an autopsy series and whether the patient had died of cardiovascular disease. Again, it seems likely that measures to reduce lead exposure in the U. S. population will lead to small, but important, reductions in cardiovascular risk.

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